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Apoptin-associating protein

Abstract

The invention relates to the field of apoptosis. The invention provides novel therapeutic possibilities, for example novel combinatorial therapies or novel therapeutic compounds that can work alone, sequentially to, or jointly with Apoptin, especially in those cases wherein p53 is (partly) nonfunctional.

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Claims

What is claimed is:

1. An isolated or recombinant nucleic acid or functional equivalent or functional fragment thereof encoding an Apoptin-associating proteinaceous substance that localizes in the nucleus of a cell and induces apoptosis.

2. The nucleic acid according to claim 1, wherein said Apoptin-associating proteinaceous substance co-localizes with Apoptin.

3. The nucleic acid according to claim 1, wherein said nucleic acid is derived from a cDNA library.

4. The nucleic acid according to claim 3, wherein said cDNA library comprises human cDNA.

5. The nucleic acid according to claim 1, wherein said nucleic acid hybridizes to a nucleic acid molecule encoding an Apoptin-associating proteinaceous substance as shown in FIGS. 1 or 5.

6. The nucleic acid according to claim 1, wherein said nucleic acid is at least 60% homologous to a nucleic acid molecule or to a functional equivalent or functional fragment thereof encoding an Apoptin-associating proteinaceous substance as shown in FIGS. 1 or 5.

7. A host cell comprising a nucleic acid according to claim 1.

8. A vector comprising a nucleic acid according to claim 1.

9. The vector according to claim 8, wherein said vector comprises a gene-delivery vehicle.

10. A host cell comprising a vector according to claim 8 or 9.

11. The host cell according to claim 10, wherein said host cell is a eukaryotic cell

12. The host cell according to claim 11, wherein said host cell is a yeast cell or a vertebrate cell.

13. An isolated or recombinant Apoptin-associating proteinaceous substance that localizes to the nucleus of a cell and induces apoptosis.

14. The proteinaceous substance according to claim 13, wherein said proteinaceous substance is encoded by a nucleic acid that is at least 60% homologous to a nucleic acid depicted in FIGS. 1 or 5.

15. The proteinaceous substance according to claim 13, wherein said proteinaceous substance comprises

at least a part of an amino acid sequence as shown in FIGS. 2 or 6 or a functional fragment thereof.

16. An isolated or synthetic antibody that specifically recognizes a proteinaceous substance or functional equivalent or functional fragment thereof, wherein said proteinaceous substance comprises at least a part of an amino acid sequence as shown in FIGS. 2 or 6 or a functional fragment thereof.

17. A proteinaceous substance that is specifically recognized by an antibody according to claim 16, wherein said proteinaceous substance localizes to the nucleus of a cell and induces apoptosis.

18. A method of inducing apoptosis, said method comprising: providing a host cell with a nucleic acid that encodes a proteinaceous substance that comprises at least a part of an amino acid sequence as shown in FIGS. 2 or 6 or a functional fragment thereof, whereby apoptosis is induced.

19. The method according to claim 18, wherein said apoptosis is p53-independent.

20. The method according to claim 19, further comprising: providing said host cell with a nucleic acid encoding Apoptin or a functional equivalent or fragment thereof.

21. A method of inducing apoptosis, said method comprising: providing a host cell with a proteinaceous substance that comprises at least a part of an amino acid sequence as shown in FIGS. 2 or 6 or a functional fragment thereof, whereby apoptosis is induced.

22. The method according to claim 21, wherein said apoptosis is p53-independent.

23. The method according to claim 22, further comprising: providing said host cell with an Apoptin or a functional equivalent or fragment thereof.

24. A pharmaceutical composition comprising a nucleic acid that is at least 60% homologous to a nucleic acid sequence as shown in FIG. 1 or FIG. 5, wherein said pharmaceutical composition induces apoptosis.

25. The pharmaceutical composition according to claim 24 further comprising a nucleic acid encoding Apoptin or a functional equivalent or fragment thereof or Apoptin or a functional equivalent or fragment thereof.

26. The pharmaceutical composition according to claim 24 wherein said apoptosis is p53-independent.

27. A method of treating a disease where enhanced cell proliferation or decreased cell death is observed in an individual in need thereof, said method comprising: providing said individual with a pharmaceutical composition comprising a nucleic acid that is at least 60% homologous to a nucleic acid sequence depicted in FIG. 1 or FIG. 5, whereby said disease where enhanced cell proliferation or decreased cell death is observed is treated.

28. The method according to claim 27, wherein said pharmaceutical composition further comprises a nucleic acid encoding Apoptin or a functional equivalent or fragment thereof.

29. A method of treating a disease where enhanced cell proliferation or decreased cell death is observed in an individual in need thereof, said method comprising: providing said individual with a pharmaceutical composition comprising a proteinaceous substance that comprises at least part of the amino acid sequence depicted in FIG. 2 or FIG. 6, whereby said disease where enhanced cell

proliferation or decreased cell death is observed is treated.

30. The method according to claim 29, wherein said pharmaceutical composition further comprises an Apoptin or a functional equivalent or fragment thereof.

31. The method according to claim 27 or 29, wherein said disease comprises a cancer or an autoimmune disease.

32. An isolated or recombinant nucleic acid encoding a proteinaceous substance comprising the amino acid sequence as shown in FIG. 7.

33. A diagnostic assay for identifying a putative effector of the activity of the proteinaceous substance encoded by a nucleic acid as shown in FIG. 5, said assay comprising: bringing into contact a proteinaceous substance comprising amino acids 185-304 of the amino acid sequence shown in FIG. 6 with said effector, and determining the binding of said effector.

Description

TECHNICAL FIELD

[0001] The invention relates to the field of apoptosis.

BACKGROUND

[0002] Apoptosis is an active and programmed physiological process for eliminating superfluous, altered or malignant cells (Earnshaw, 1995, Duke et al., 1996). Apoptosis is characterized by shrinkage of cells, segmentation of the nucleus, condensation and cleavage of DNA into domain-sized fragments, in most cells followed by internucleosomal degradation. The apoptotic cells fragment into membrane-enclosed apoptotic bodies. Finally, neighbouring cells and/or macrophages will rapidly phagocytose these dying cells (Wyllie et al., 1980, White, 1996). Cells grown under tissue-culture conditions and cells from tissue material can be analysed for being apoptotic with agents staining DNA, as e.g. DAPI, which stains normal DNA strongly and regularly, whereas apoptotic DNA is stained weakly and/or irregularly (Noteborn et al., 1994, Telford et al., 1992).

[0003] The apoptotic process can be initiated by a variety of regulatory stimuli (Wyllie, 1995, White 1996, Levine, 1997). Changes in the cell survival rate play an important role in human pathogenesis of diseases, e.g. in cancer development and auto-immune diseases, where enhanced proliferation or decreased cell death (Kerr et al., 1994, Paulovich, 1997) is observed. A variety of chemotherapeutic compounds and radiation have been demonstrated to induce apoptosis in tumor cells, in many instances via wild-type p53 protein (Thompson, 1995, Bellamy et al., 1995, Steller, 1995, McDonell et al., 1995).

[0004] Many tumors, however, acquire a mutation in p53 during their development, often correlating with poor response to cancer therapy. Certain transforming genes of tumorigenic DNA viruses can inactivate p53 by directly binding to it (Teodoro, 1997). An example of such an agent is the large T antigen of the tumor DNA virus SV40. For several (leukemic) tumors, a high expression level of the proto-oncogene Bcl-2 or Bcr-abl is associated with a strong resistance to various apoptosis-inducing chemotherapeutic agents (Hockenberry 1994, Sachs and Lotem, 1997).